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[RUSH] **MESSAGE:** Illegible text on pages 282 + 283.

Please Resolve.

Thank You,
NW3

[XRUSH] **RESPONSE:** New pages 282+283 attached.

INITIALS: KAT

NOTE: This form will be included as part of the official USPTO record, with the Response document coded as XRUSH.

REV 10/04

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Fax

To:	Ms. Lacie Hawkins	**From:**	SW Gorman
Fax:	703-746-4638	**Pages:**	including cover sheet 3
Phone:	703-308-9250	**Date:**	11 August 2005
Your Ref.:	10/015,184	**Our Ref.:**	1718-0194PUS1
Re:		**CC:**	

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• **Comments:**

Dear Ms. Hawkins,

Please find attached pages 282 & 283 from the 10/015,184 application.

Page 282 begins with ^{31}P-NMR .... Example A-4

Page 283 begins with a) 4-Benzyloxycarbonylamino ....

Many Thanks,

Susan Gorman

^{31}P-NMR ($CDCl_3$+5%CD_3OD)(H_3PO_4 reference): δ 14.9 (s).

Example A-4

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (383 mg, 1 mmole) was esterified by the method described in Example A-3-a to yield 184 mg of title compound. R_f (20%MeOH/$CHCl_3$) 0.20 (at the center of oval spot from baseline).

^{1}H-NMR ($CDCl_3$+ 1%CD_3OD): 7.27 (m, 15H), 5.62 (m, 4H), 5.15-4.72 (m, 8H), 4.32 (m, 2H), 3.08 (m, 2H), 2.16-1.73 (m, 6H), 0.88 (m, 24H). ^{31}P-NMR ($CDCl_3$+1%CD_3OD)(H_3PO_4 reference): δ 15.5 (s).

b) 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester.

4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, di (2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyryloxymethyl) ester (184 mg, 0.166 mmol) was hydrogenated over Pd-black (71 mg) by the method of Example A-1-b, to give the title compound as the triacetate as a white solid (95 mg).

^{31}P-NMR ($CDCl_3$+5%CD_3OD)(H_3PO_4 reference): δ 14.6 (s).

Example A-5

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, mono (2-methyl-2-(L-valyloxymethyl) propionyloxymethyl) ester.

a) 4-Benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, tribenzyl mono (2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionyloxymethyl) ester.

To a solution of 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid (1.54 g, 4 mmole) in dry N,N-dimethylformamide (24 ml), heated at 50 °C, was added diisopropylethylamine (2.78 ml, 16 mmole), followed by dropwise addition of benzylbromide (1.9 ml, 16 mmole). After stirring under argon for 4 h, the solution was concentrated on rotavapor and treated with ethyl acetate (20 ml). Crystals were filtered off and the filtrate was extracted with brine. The organic phase was filtered through anhydrous sodium sulfate and evaporated. The 4-benzyloxycarbonylamino-1-hydroxybutylidene-1,1-bisphosphonic acid, tribenzylester was isolated by silica gel column chromatography (2-4, 7-10, 15-20% ethanol in dichloromethane). The pure fractions containing the pure triester were pooled together and evaporated. The residue was then dissolved in ethyl acetate and the solution extracted three times with 2M aqueous solution of citric acid. Triester (990 mg); R_f (20%MeOH/ $CHCl_3$) 0.15 (at the center of oval spot from baseline);

^{31}P-NMR ($CDCl_3$) (H_3PO_4 reference): δ 20.4(d), 13.3 (d); ^{1}H-NMR ($CDCl_3$): 7.35-7.10 (m, 20H), 5.20-4.91 (m, 8H), 4.60 (br, 1H), 3.00 (m, 2H), 2.12-1.75 (m, 4H).

b) Dried tribenzyl ester (395 mg) was dissolved in dry N,N-dimethylformamide (3 ml), followed by addition of diisopropylethylamine (99 ml) and a solution of iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate (737 mg) in N,N-dimethylformamide (1 ml). After stirring under argon for 4 h at 30 °C, the solution was concentrated to dryness on rotavapor and treated with ethyl acetate (10 ml). Crystals were filtered off and the filtrate was extracted with brine brine containing a small amount of sodium thiosulfate. The organic phase was filtered through anhydrous sodium sulfate and evaporated. The title compound (84 mg) was isolated by silica gel column chromatography (1, 2, 3% ethanol in dichloromethane). R_f (2%MeOH/ $CHCl_3$) 0.60;